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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

ROBINSON, H

ART UNIT	PAPER NUMBER
1653	10

DATE MAILED: 07/12/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/341,009	Applicant(s) Wu et al.
	Examiner Hope Robinson	Group Art Unit 1653

Responsive to communication(s) filed on May 26, 2000

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 18-31 is/are pending in the application.

Of the above, claim(s) 18-20 is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 21-31 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) PCTCA98/01010.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). 10

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

1. Applicant's election with traverse of Group I in Paper No. 8 is acknowledged. The traversal is on the ground(s) that groups I-III claims not be restricted and all claims are examined since the invention exhibits corresponding special technical feature and unity of invention is present. It is noted that applicant has elected the species lactocystin and rapamycin be examined. Applicant's arguments have been fully considered but are not persuasive because proteasome inhibitors are well known in the prior art therefore, groups I-III do not appear to have a contribution over the prior art, therefore, lack unity of invention. It is noted that applicant has canceled Claims 1-17 and that Claims 18-20 and New Claims 21-31 are pending. However, Claims 18-20 will not be examined as drawn to a non-elected group. Applicant in Paper No. 8 indicate that Group I is elected, and Claims 18-20 as set forth in the Restriction Requirement mailed March 8, 2000, are drawn to a different invention, Group IV, classified in 435/4. Whereas, the elected invention is classified in 514/19. Only Claims 21-31 which applicant intends to replace the canceled claims 1-9 in the elected group will be examined in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

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make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 21-31 are rejected under 35 U.S.C. 112 first paragraph, because the specification, while being enabling for a method of inhibiting T and B cell proliferation with lactacystin (see page 13+) and only for treating cells with lactacystin, does not reasonably provide enablement for a method of reversing the ongoing action of any activated blood cells, comprising administering an effective amount of a proteasome inhibitor to an individual in need of such treatment nor for the claimed "analog thereof".

The specification is absent data or examples of a method of reversing the ongoing action of activated blood cells with the administration of a proteasome inhibitor to an individual. Furthermore, there is no demonstration of a method employing analogs thereof for lactacystin. In addition, neither the claims nor the specification provides a clear definition as to what ongoing action of activated blood cells is being reversed by the claimed method. Further, it is unclear as to what the desired effect is once the treatment is administered. The specification is also absent data with a showing of treatment for an individual suffering from septic shock, adverse immune response or inflammation. Claim 24 recites the co-administration of an immunosuppressive drug, yet the disclosure does not provide any dosage information or data on the use or the effect of the drug. In view of the foregoing, the specification is not enabled because it does not provide adequate guidance to be able to practice the claimed invention. In addition, since the specification is absent exemplification of the claimed invention and to examine all the possible "analogs

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thereof" would require undue experimentation. Therefore, at the time the application was filed, would not have taught one skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) lists the factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include but are not limited to: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art, (g) the predictability of the art; and (h) the breadth of the claims.

3. Claims 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 30 and 31 recite "lactocystein" and there is no apparent antecedent basis in the specification or original claims as filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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4. Claims 21-31 are rejected under 112, second paragraph as failing to distinctly point out the subject matter applicant regards as his invention.

Claim 21 is rejected as being indefinite because the claim recites “a method for reversing the ongoing action of activated blood cells” without defining what action is being reversed. Further the claim is indefinite for reciting “administering an effective amount of a proteasome” since the quantity is undefined, and the metes and bounds of the claim is unclear with this recitation. It is also unclear as to whether this treatment will serve as a cure or what effect it will produce in the individual. Additionally, it is not clear what condition the individual is being treated for or what disease. The dependent claims are included in this rejection.

Claim 25 is indefinite because the claim recites cyclosporin A, rapamycin and FK506 and applicant has elected one specie, “rapamycin”.

Claim 27 is indefinite because it depends from Claim 26 which indicates that the activated blood cells experienced apoptosis (cell death), therefore, Claim 27 is ambiguous since it asserts that the cells are undergoing inhibition of energy and oxygen supply which implies that they are not yet dead.

Claims 30 and 31 are indefinite because the claims recites “lactocystein” which is misspelled, the correct spelling is “lactacystin”.

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Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 21-24, 30 and 31 are rejected under 35 U.S.C. 102 (b) as being anticipated by Schreiber et al. (WO 96/32105, October 17, 1996).

Schreiber et al. disclose compounds used to treat conditions mediated directly by the proteolytic function of the proteasome such as muscle wasting, or mediated indirectly via proteins which are processed by the proteasome such as NF- κ B. Schreiber et al. disclose that the proteasome participates in the rapid elimination and post-translational processing of proteins involved in cellular regulation, intercellular communication and the immune response. Further, Schreiber et al. disclose a treatment which includes reversing, reducing or arresting the symptoms, clinical signs and underlying pathology of a condition in a manner to improve or stabilize the subject's condition (see page 81).

In addition, the reference discloses that treatment comprises administering to a subject an effective amount of a compound (see page 82). Furthermore, Schreiber et al. teach a method for treating inflammation, wherein the method includes administering to a subject an effective anti-inflammatory amount of a pharmaceutical composition containing a compound of a formula.

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Inflammation can be a primary or secondary response to surgery (i.e. transplantation), infection etc. (see page 85). Chronic or acute inflammation can result from transplantation rejection (i.e. tissue grafts, skin grafts, organ of any type etc.) or autoimmune diseases (see page 87). Schreiber et al. also disclose that the preferred compounds and compositions include various lactacystin thioesters, and lactacystin β -lactone analogs, including the β -lactone itself. Therefore, the limitations of the claims are met by the Schreiber et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

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made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

7. Claims 21-31 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Schreiber et al. (WO 96/32105, October 17, 1996) in view of Armistead et al. (U.S. Patent No. 5,665,774, March 8, 1993) and Imajoh-Ohmi et al. (Biochemical and Biophysical Research Communications, vol. 217, No. 3, pages 1070-1077, 1995).

Schreiber et al. disclose compounds used to treat conditions mediated directly by the proteolytic function of the proteasome such as muscle wasting, or mediated indirectly via proteins which are processed by the proteasome such as NF- κ B. Schreiber et al. disclose that the proteasome participates in the rapid elimination and post-translational processing of proteins involved in cellular regulation, intercellular communication and the immune response. Further, Schreiber et al. disclose a treatment which includes reversing, reducing or arresting the symptoms, clinical signs and underlying pathology of a condition in a manner to improve or stabilize the subject's condition (see page 81).

In addition, the reference discloses that treatment comprises administering to a subject an effective amount of a compound (see page 82). Furthermore, Schreiber et al. teach a method for treating inflammation, wherein the method includes administering to a subject an effective anti-inflammatory amount of a pharmaceutical composition containing a compound of a formula. Inflammation can be a primary or secondary response to surgery (i.e. transplantation), infection

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etc. (see page 85). Chronic or acute inflammation can result from transplantation rejection (i.e. tissue grafts, skin grafts, organ of any type etc.) or autoimmune diseases (see page 87).

Schreiber et al. also disclose that the preferred compounds and compositions include various lactacystin thioesters, and lactacystin β -lactone analogs, including the β -lactone itself. Schreiber et al. do not expressly teach the use of the immunosuppressive drug rapamycin.

Armistead et al. disclose immunosuppressive drugs to prevent or significantly reduce graft rejection in bone marrow and organ transplantations and for use in the treatment of a wide variety of autoimmune diseases in humans and other mammals (see abstract). Armistead et al. disclose a method of administering immunosuppressants FK-506, cyclosporin A and rapamycin to control or reverse chronic rejection of allografts in a transplantation patient (see column 9). Armistead et al. do not expressly teach apoptosis of the activated blood cells.

Imajoh-Ohmi et al. disclose that lactacystin, originally isolated from a microbe as an inducer of neuritogenesis, targets the catalytic β -subunit of the proteasome, and arrests the cell cycle. Further, lactacystin is said to induce apoptotic cell death in human monoblastic cells. In addition, Imajoh-Ohmi et al. disclose that inhibition of the proteasome during proliferation results in apoptotic cell death and that the proteasome is a key enzyme in the course of the cell cycle that destines the cell to proliferate, differentiate or die. The reference discloses that when apoptosis was induced with TNF- α condensation of cytoplasm was seen followed by formation of apoptotic bodies and nuclear fragmentation. Lactacystin treated cells exhibited the same compact features

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of nuclear chromatin in dying cells. For example, a ladder like DNA breakdown and internucleosomal DNA fragmentation (i.e. cleavage and condensation).

In view of the foregoing, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention as a whole based on the teachings of the above references. One would be motivated to combine the references because Schreiber et al. disclose: that proteasome participates in the immune response, a treatment which includes reversing, reducing or arresting the symptoms of a condition in a manner to improve or stabilize the subject's condition, a method for treating inflammation, wherein the method includes administering to a subject an effective anti-inflammatory amount of a pharmaceutical composition containing a compound, that chronic or acute inflammation can result from transplantation rejection (i.e. tissue grafts, skin grafts, organ of any type etc.) or autoimmune diseases and that the preferred compounds and compositions include various lactacystin thioesters and lactacystin β -lactone analogs. In addition, the secondary references by Armistead et al. (disclose the method of using cyclosporin A, rapamycin and FK-506 for autoimmune diseases and graft rejection) and Imajoh-Ohmi et al. (disclose the ability of lactacystin to induce apoptotic cell death in human monoblastic cells and the morphological and biochemical changes the cell undergoes before dying), teach the limitations not covered by Schreiber et al. Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

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Conclusion

8. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope Robinson whose telephone number is (703) 308-6231. The examiner can normally be reached on Monday-Friday from 9:00 am to 5:30 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S. F. Low, can be reached at (703) 308-2923.

Any inquiries of a general nature relating to this application should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. The official fax phone number for Technology Center 1600 is (703) 308-4242. Please affix the examiner's name on a cover sheet attached to your communication should you choose to fax your response. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

Hope Robinson, MS

Patent Examiner

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